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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,195	09/14/2001	Martin John Glenton Hughes	GJE-71	7256

23557 7590 04/21/2004

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,195	HUGHES ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-31* is/are pending in the application.

4a) Of the above claim(s) *13-24,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *13-31* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-17-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed 2-2-04 has been entered into the record. The preliminary amendment filed June 15, 2001 has been entered into the record. Claims 1-12 have been cancelled. Claims 13-31 have been added.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in GB 9828346.8 on 22 December 1998 and GB 9908321.4 on 12 April 1999. It is noted, however, that applicant has not filed a certified copy of the GB applications application as required by 35 U.S.C. 119(b).

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Information Disclosure Statement

The information disclosure statement filed 9-17-01 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election of Group 13, claims 25-29, in part, as drawn to therapy using MS10 peptides in the Paper filed 2-2-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 13-24 and 30-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claim Objections

Claims 25-29 are objected to because of the following informalities: The claims include non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method for the treatment or prevention of a condition associated with bacterial infection by administering to a patient in need of such treatment or prevention an effective amount of a peptide encoded by a gene obtainable from a Group B *Streptococcus* wherein the peptide is MS10, a homologue or a functional fragment thereof. The specification teaches a single nucleic acid (SEQ ID NO:11) encoding a "MS10" polypeptide of SEQ ID NO:12 from the Group B Streptococcal strain M732. SEQ ID NO:12 is described as having homologues in *Streptococcus mutans*, *Nicotiana plumb*, *Pisum sativum* and *Zea mays*. The homologues allegedly have the activity of nonphosphorylating, NADP-Dependent Glyceraldehyde-3-Phosphate Dehydrogenase (see specification page 10, lines 18-32). The specification does not place any structure, chemical or functional limitations on the variants of MS10. The recitation of "MS10" does not convey a common structure or function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the MS10 protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the therapeutic function alone is insufficient to describe the genus of MS10 peptides, fragments, and homologues that function equivalently. One of skill in the art would reasonable conclude that the disclosure of a single SEQ ID NO:12, fails to provide a representative number of species of MS10 to describe the claimed genus. Applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of variants in structure and function of any such polypeptide that has the claimed properties of MS10. The genus of peptides with

the claimed function is substantial and highly variant because the polypeptides do not have a common structure and function. The recitation of "MS10" does not convey a common structure nor a common function. The generic MS10 polypeptide sequences that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the highly variant genus of single function polypeptides (therapeutic) and one skilled in the art would not recognize that applicants had possession of the genus of claimed polypeptides for use in the therapeutic method as instantly claimed. Further, Applicants have not described nor disclosed the gene which encodes the "MS10" protein. A functional bacterial gene encompasses much more than a protein coding region (see Davis et al., Microbiology, page 267). A bacterial gene is conventionally associated with positive and negative controlling elements such as promoters and repressors in a concordantly regulated transcription unit called an operon, without which, no protein is expressed. The specification fails to describe the functional gene *per se* (i.e., operon) and which applicants have intended to be encompassed by the "gene" language of the instant claims as set forth *supra*. In a bacterial genome, the recitation of "gene", includes regulatory sequences which are essential to the operation and function of the structural gene in the operon. These regulatory and other gene sequences that are not described, are essential to the function of the structural MS10 gene within the bacteria and are therefore essential elements. Such sequences fail to have an adequate written description of the gene for MS10 and the particular disclosed specie, Group B Streptococcal strain M732. As such, there is no written description of any MS10 gene in the specification as filed. There is no written description of the genus of highly variant genus of genes in the specification as filed. The term "MS10" does not provide written description of the missing subject matter and does not convey any particular structure of a gene or of a particular genus of genes. As such, the instant specification fails to convey a representative number of genes encoding a representative number of variants, homologs

and functional fragments to demonstrate that Applicants were in possession of the claimed invention at the time of filing.

Claims 25-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of treatment or prevention of a condition associated with bacterial infection, wherein said method comprises administering to a patient in need of such treatment or prevention, an effective amount of a peptide encoded by a polynucleotide sequence wherein in said polynucleotide sequence comprises a gene, obtainable from a Group B Streptococcus, wherein the peptide is MS10, a functional fragment thereof or an homologue thereof or wherein the peptide comprises SEQ ID NO:12 and wherein the infection is a urinary tract infection.

The claims are drawn to therapeutic or methods of prevention of conditions associated with bacterial infection. The specification teaches that such prevention occurs by means of generating an immune response (specification pages 2-3) and that such language specifically includes the prophylactic effect of vaccines. The specification fails to provide evidence as to what conditions are treated or prevented by the administration of MS10. The teachings of the specification are devoid of any teaching that animals in a normal infection generate antibodies that bind the MS10 polypeptide(s), fragments or homologs as claimed and therefore is not clear that the polypeptides of the invention are capable of generating an antibody response during a normal course of infection. Further, the specification fails to teach that any immune response generated upon injection by the claimed Group B *Streptococcus* MS10 peptides, fragments thereof, or homologs alone provide for a protection against infection or treat or prevent a condition associated with bacterial infection as instantly claimed. Vaccines by definition trigger an

immunoprotective response in the host vaccinated and mere antigenic response is insufficient. Applicants have not demonstrated that any immune response generated is capable of treating any condition associated with all forms of bacterial infection. Further, the specification fails to teach that the MS10 peptides generate mucosal antibodies (i.e. sIgA) in a sufficient amount to treat or prevent a urinary tract infection. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed polypeptides, fragments thereof or homologs does in fact confer protection from infection, as is requisite of a vaccine composition or provides any therapeutic benefit to treat any condition associated with any bacterial infection. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to that the presence of antibodies that bind MS10 or SEQ ID NO:12 or homologs as claimed provides for protection from infection or treatment of any condition. While the specification teaches that the MS10 polypeptide of SEQ ID NO:12 has homology to the nonphosphorylating, NADP-Dependent Glyceraldehyde-3-Phosphate Dehydrogenase , the art does not recognize the homologs as therapeutics or prophylactic vaccines capable of conferring protection on an immunized host from any condition associated with bacterial infection. The specification fails to teach that the claimed polypeptide or fragment is able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize any homologs or other similar proteins as a therapeutic or protective vaccine for a condition associated with bacterial infection. The dictionary definition of vaccine is "A

prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity)." (The Dictionary of Immunology, Herbert et al eds, Academic Press, 1995) would clearly realize the critical deficiency of this specification with respect to vaccines. There is absolutely no demonstration of protective immunity upon administration in any animal model of disease. Such is required by the common meaning as demonstrated by the dictionary definition and is reiterated in Plotkin et al, as is cited in the previous office action. Further, none of the art recognized homologs have been demonstrated to have vaccine properties with the homologous microorganism. The art is replete with evidence that the ability to produce an antibody (immunogenicity) is insufficient to correlate with protection from infection. See for example Feng et al (Infection and Immunity, 64(1):363-365, 1996) that teaches that P55, is an immunogenic but nonprotective 55-kilodalton *Borrelia burdorferi* protein in murine lyme disease. Further, the art recognizes that immunogenicity does not correlate with treatment or protection from disease (Chandrashekar et al U.S. Patent 6,248,329, column 1, lines 34-41). Even if one were to demonstrate the protection with SEQ ID NO:12, the specification lacks specific teachings of where and how one could alter SEQ ID NO:12 and still get treatment/protection from disease. The retention of the specificity following one or more amino acid substitutions in a polypeptide is another factor that has been shown to be unpredictable in the art. For instance, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993) taught that "[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure" in case of a meningococcal polypeptide (see abstract). Similarly, McGuinnes *et al.* (*Lancet* 337: 514-517, March 1991) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria*

meningitidis of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate (see abstract and page 514). For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool." The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510). In the absence of a teaching of the claimed polypeptides are effective in prevention or treatment of a condition associated with bacterial infection, the specification is not be enabled for therapeutics/vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed. For the foregoing reasons, one skilled in the art would have ample reason to doubt the ability to use MS10, fragments thereof and homologs thereof as a method of treatment or prevention of a condition associated with bacterial infection as instantly claimed.

Claims 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 25-29, the claims are indefinite in the use of the term "condition associated with bacterial infection". The condition associated with bacterial infection is not set forth nor defined in the specification as filed. As such, one skilled in the art would not be able to tell if they were infringing upon the claimed method since the metes and bounds of a condition associated with bacterial infection is not set forth in the claims or the specification. Further, the claims are indefinite with respect to the name designation of "MS10". This designation does not define any particular protein structure or function such that one skilled in the art would know if they were infringing upon the claimed invention. As such, the metes and bounds of MS10 peptides, fragments and homologues are not clearly defined in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country r in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-29 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Itoh et al, (Microbiology and Immunology, 30(4):297-306, 1986).

The claims are drawn to a method of treatment or prevention of a condition associated with bacterial infection, wherein said method comprises administering to a patient in need of such treatment or prevention, an effective amount of a peptide encoded

by a polynucleotide sequence wherein in said polynucleotide sequence comprises a gene, obtainable from a Group B *Streptococcus*, wherein the peptide is MS10, a functional fragment thereof or an homologue thereof or wherein the peptide comprises SEQ ID NO:12 and wherein the infection is a urinary tract infection.

Itoh et al teach immunization of maternal mice using whole cell vaccines from group B *Streptococci* and the passive transfer of protective antibodies to neonatal mice. The immunization of the maternal mice with whole cell vaccines anticipates the claimed invention in view of the fact that the administered MS10 peptides, fragments or homologs thereof are not purified and the whole cell inherently contains the gene encoding the MS10 peptide, fragment or homolog absent convincing factual evidence to the contrary.

Claims 25-29 are rejected under 35 U.S.C. 102(b) as anticipated by Ichiman et al (Canadian Journal of Microbiology 28(7):726-732, 1982).

Ichiman et al teach active immunization of mice with whole cell vaccine of type Ia Group B *Streptococci* protected against challenge. The immunization of the mice with whole cell vaccines anticipates the claimed invention in view of the fact that the administered MS10 peptides, fragments or homologs thereof are not purified and the whole cell inherently contains the gene encoding the MS10 peptide, fragment or homolog absent convincing factual evidence to the contrary.

Status of the Claims

Claims 25-29 stand rejected. Claims 13-24 and 30-31 are withdrawn from consideration as being drawn to non-elected inventions.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-F 6:30 pm - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645